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THE MANAGEMENT OF THE LATE AND LATENT SYPHILITIC

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THE MANAGEMENT AND TREATMENT OF THE LATE
AND LATENT SYPHILITIC

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The management and treatment of the late and latent syphilitic is a subject that I have long felt should be discussed by this Society. I can lay no claim to any special knowledge which would enable me to speak with more authority than that of my fellow members, and I am putting forward my views in all humility in the hope that, before the end of this meeting, we may all learn something from the pooling of our experience, for this certainly is not a subject upon which anyone of us can afford to hold bigoted views.

Although the clinics in which most of us practice were originally subsidized by the Government for the diagnosis and treatment of the venereal diseases in their more acute and infectious stages, not one of us, even if it were possible, would care to practice a "split speciality" and to degenerate into professional "spirochaete spotters" and "injectioneers" of the appropriate specifics. It is because the Ministry of Health has always allowed us to care for the late syphilitic in our clinics, and because our professional colleagues continue to regard us as syphilologists in the widest sense of the word, that cases of late and latent syphilis continue to be a cumulative charge on our time, accommodation and skill.

These patients usually come under our care in one of the following ways.

- (1) An obvious or suspicious lesion or circumstance is discovered by the patient's doctor or by another specialist. This may or may not be confirmed by positive blood findings.
- (2) A routine serological test is found to be positive, as, for instance, in the case of a blood donor or of an expectant mother.
- (3) A patient who, in the past, has had inadequate treatment for early syphilis returns after a lapse of months or years, impelled by an uneasy conscience, sometimes made still more uneasy by propaganda.
- (4) A syphilitic "family skeleton" is unearthed, and the anxious spouse, parent, brother or sister comes to us for help.

TREATMENT OF LATENT SYPHILIS

Obvious late activity almost invariably is preceded by a varying period of apparent latency, so that it is convenient to commence with latent syphilis and to discuss first its treatment and management.

Diagnosis

The diagnosis of latent syphilis is one of exclusion and is always difficult and sometimes impossible to make with accuracy. It will depend largely upon the clinical experience of the examining doctor, upon negative results of radiological and cerebrospinal fluid examinations, and upon the verification by repetition of positive blood findings. All this will take time, and fortunately, except in the

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case of the expectant mother, there is usually no need for haste. Repetition of the blood tests may show that a technical (or even a clerical) error has occurred in the clinic or the laboratory. Careful history taking may bring to light a probable date of infection or some circumstances pointing to a congenital source. A meticulous clinical examination may reveal the fact that the treponema is still active and may provide valuable information on the duration of infection.

Treatment

Supposing, however, that all efforts to establish the fact of activity are fruitless, that blood tests remain unequivocally positive on repetition over a period of at least a month, and also that there is not any recent history of malaria or infectious mononucleosis, what is to be done about treatment? This will depend upon whether, after all the evidence has been carefully weighed, the condition is considered to be one of early, medium or late latency. My own definitions of these stages are somewhat different from those set out in standard text-books and I do not think that it is advisable or possible to designate them accurately.

Early latency: cases in which the history suggests that the infection was acquired during the previous three or up to five years.—In these cases the patient must be treated strenuously. The amount of treatment given should never be less than that which is considered to be necessary for a case of late secondary syphilis. Should serological improvement take place during treatment, this fact will be confirmatory evidence that the infection is comparatively recent and, in my view, will be a strong point in favour of continuing treatment well beyond the time at which complete serological reversal ultimately occurs. At this point I should like to say that it is my invariable practice to commence treatment in all cases of late or latent syphilis (even supposedly early latent cases) with bismuth alone, and not to use the arsenicals or penicillin until bismuth has been given for at least one month.

Medium latency: cases in which the history suggests that the infection is less than ten years old.—I am aware that this period could profitably be subdivided still further and that the nature and amount of treatment given to patients at one or other end of the scale will differ substantially. The point that I wish to make is that all persons in this group also must be treated and treated strenuously. When I say strenuously, however, I do not mean that the treatment should be prolonged unduly; provided that it is not interrupted by side effects or default, I should consider that 2 years should usually see the end of it, and that this period probably could be shortened considerably if penicillin were used in conjunction with the time-honoured drugs. Neuro-recurrence is extremely unlikely to take place if the cerebrospinal fluid findings are negative before treatment is commenced; but it is as well to see that they remain so for a year or two after it is finished. In all other cases I consider it to be usually wrong to attempt to achieve serological reversal, although I admit that, when improvement occurs in the course of treatment, I sometimes yield to the temptation to prolong it for more than two years. I can remember but a very few isolated instances in which this decision has been rewarded with complete success; in the great majority this has not occurred; in not a few, treatment has been brought to an end brusquely by the intervention of jaundice or dermatitis.

Strenuous treatment is indicated particularly for women of childbearing age, and subsequent treatment during each pregnancy should always be counselled, although I think that the intensity of this can be diminished progressively after each successful pregnancy, resulting in the birth of a healthy infant with continuously negative blood reactions.

Late latency: cases in which the history or the age of the patient suggest that the infection is over ten years old.—In these cases considerations of age and sex are paramount. The untreated woman of childbearing age with positive blood reactions will always be a menace and invariably should be treated. Strenuous treatment for at least a year is advisable, and treatment during any future pregnancies must be insisted upon. The fact that the woman is already the mother

of healthy children, although a pointer in favour of her non-infectivity, will not guarantee it.

In all other cases in this group, treatment should be on an "insurance" basis. To set about attempting to reverse a positive serology by giving course after course of arsenicals is, in my view, both unjustifiable and potentially dangerous. Opinions as to what may be considered as adequate "insurance" treatment doubtless will differ. Most of us are familiar with the views of the American syphilologists, Moore, Stokes and others, whose figures have contributed largely to the reports of the Cooperative Clinical Group (Stokes and his collaborators). I did not read these reports carefully until comparatively late in my own career, but I was then agreeably surprised to discover how closely they tallied with my own experience. My own practice has been to give these patients—or attempt to give them—about 15 grammes of a trivalent arsenical and 6 grammes of bismuth over a period of about 10 months. Whether this is given by concurrent, intermittent or continuous methods is, I believe, immaterial. I make it a rule to give about 6 bismuth injections before commencing the arsenical treatment. There is always an element of risk in giving arsenicals or penicillin from the outset. Many cases of syphilitic aortitis are impossible to diagnose, and a complaint of even slight praecordial pain following an injection of one of these powerful medicaments, although, admittedly, it might have no significance, would shake the resolution of most of us.

Assessment of duration of infection.—In many—possibly most—latent syphilitics, it is impossible even to guess at the duration of infection. Most of us, perhaps, are a little too much inclined to date it to the years of early adult life, or to a period spent in the armed Forces. Occasionally one is deceived; the middle-aged or even the elderly may contract syphilis, and early signs frequently pass unnoticed in women.

Latent congenital syphilis.—In addition, the possibility of a congenital infection cannot be overlooked. I recollect one instance in which chance comment on the edentulous condition of a middle-aged woman led to her volunteering the information that she had had her front teeth extracted recently, not because they were bad, but because of the unsightly notches in them. Quite recently I came across a patient whose upper central incisors had been shortened for a similar reason. The less classical stigmata of congenital syphilis, which have probably been rather over-emphasized by Fournier and other French authorities (Fournier; Fournier and Perret), may (when not too credulously appreciated) provide clues which may lead one to investigate the history and possibly the sera of the patient's brothers and sisters. Examples of these signs are aplasia and gapping of the teeth, microdentism, varying degrees of facial asymmetry, malformations of the aural pinnae, minor degrees of frontal bossing, increased carrying-angle of the elbow joint and, particularly, that almost indescribable slight flattening of the upper part of the face, which we all know so well.

In apparently latent congenital syphilis, the importance of a meticulous clinical examination, including ophthalmoscopy, examination of the cerebrospinal fluid and, in adolescents, skiagrams of the long bones, will be appreciated. In adults the heart and great blood vessels should be examined radiologically, although it is extremely rare for any abnormality to be found. It is, as far as I know, an unsolved riddle why cardiovascular syphilitic disease all but never seems to occur in congenital infections.

The object of treatment is to prevent the future development of active lesions. In the presence of a negative reaction of the cerebrospinal fluid, interstitial keratitis and deafness are the two most frequent possibilities. These manifestations usually occur before the age of 15 years, but occasionally not until well on in the twenties or later. At whatever age treatment for late or latent congenital syphilis is begun, the prospect of attaining reversal of the positive serological reaction is a slender one; the majority of cases (that is to say, over 60 per cent) remain Wassermann-positive irrespective of the amount of treatment given. Moore regards it as unnecessary to continue treatment for longer than one year.

My own practice has always been to give these patients (according to their age and weight) the equivalent of three standard courses of arsenicals and bismuth, and, once this has been given, not to differentiate between males and females, and to permit marriage and childbearing without further treatment. The male congenital syphilitic can be regarded always as completely non-infectious, the female as almost certainly so. To the extent of my knowledge, no case of third-generation syphilis has ever been reported in which the mother had received minimal treatment. Thus, in the management of latent congenital syphilis, an attitude of unguarded optimism can almost always be assumed, and the gloomy biblical innuendos about "the sins of the fathers" and "the third and fourth generation"—which almost certainly did not apply to syphilis, anyhow—can be dismissed emphatically.

Management, as distinct from treatment

As soon as we have completed our investigations and have come to some conclusion on the approximate duration of infection and the nature of the treatment which we think will probably be necessary, the question arises, "What is the patient to be told?". My answer to this is "The truth". All patients, excepting the aged (for whom no treatment is thought to be necessary), or rare cases of mental instability, must have the facts, as the doctor sees them, carefully explained as soon as possible after a diagnosis is made. The word, syphilis, must not be burked, and vague allusions to a "blood condition" or some such indefinite euphemism must not be substituted in its place. If this frank truth-telling is not done, the necessity for even a reasonable period of treatment, for repeated blood tests and for life-long observation will be difficult to justify, and the later realization of the true state of affairs will cause more psychological upset than will the short sharp shock of the truth, provided that it is imparted with sympathy and optimism. I have been impressed by the bitterness with which patients have spoken of doctors who had failed to tell them exactly what was wrong, presumably in a mistaken attempt to spare their feelings.

Sero-resistance and its interpretation.—The significance and probability of sero-resistance, in spite of adequate treatment, should be explained as soon as possible to all who are in any way capable of understanding. This can be oversimplified conveniently by explaining that, whereas in early syphilis sero-resistance is probably a sign of persisting infection, in late or latent cases it is most often an indication of well established immunity. If this is not done at an early stage, the patient will inevitably associate a persisting positive blood test with lack of response to treatment, and consequently will become either dissatisfied with his doctor or apprehensive about and even despairing of his condition. The doctor must try to make the patient understand that he knows how much treatment is necessary for his particular case, and that the fact of serological fastness need not, to any extent, influence the ultimate prognosis. This is no more than the strict truth; many of us will admit that we become more anxious when the blood of a latent syphilitic suddenly reverts to negative after a comparatively small amount of treatment, for we then become uncertain as to the stage of infection and as to whether or not we should continue treatment beyond our original intention.

In medium or late latent syphilis, perhaps more than in any other condition, the doctor can afford to be optimistic, and it is undoubtedly his duty to be so. The findings of the Cooperative Clinical Group (Stokes and his collaborators), which are in line with my own experience, suggest that in 20-30 per cent only of all latent syphilitics, even if untreated, would any late manifestations of disease develop, and that treatment, even of the most moderate nature, will reduce this chance to as low a figure as 2-5 per cent. When one considers the uncertainties of everyday life, this is surely a more than reasonable hazard and one which, in almost all cases, should be minimized to the patient.

Marriage and childbearing.—Latent syphilis must not be allowed to spoil lives, but only too often it does so. One of the chief ways in which this happens is

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when the prospects of a marriage, contemplated or even arranged, are suddenly shattered on account of it: in other instances the discovery of a positive blood test in an already married person, unless the case is carefully handled, may lead to needless recriminations and sometimes even to the break-up of a home. Hardly a week passes without our advice being asked on one of these points.

Quite shortly, the line which I take is as follows. All male patients, if they are considered to be medium or late latent cases, are given permission to marry one year after the completion of their treatment, always provided that no signs of "clinical syphilis" or cerebrospinal fluid changes become apparent during this time. If early latency is a probability, periodical clinical examination for any signs of cutaneous relapse is advisable during the two years' probation given in these cases. No restriction is placed on the marriage of men with undubitably congenital stigmata. Provided that these rules are complied with, I do not think that, in most cases, it is either necessary or wise for a man to inform his fiancée of his condition. If he wants to do so, well and good; but *cui bono*? Too often the information is duly pigeon-holed and some time, at a later date, quite irrelevantly thrown in his face.

The untreated woman of childbearing age in any stage of syphilis, with the exception of the late congenital, is always a menace, and treatment is probably more than twice as necessary for her as it is for a man in the same stage. If the history in any way suggests early latency, marriage should be forbidden for two years after the completion of treatment, and then allowed only on the express understanding that further treatment is agreed to during pregnancy. As an earnest that this condition is in fact carried out, I always try to persuade the bride to inform her future husband before marriage of her condition, and I believe that the doctor should interview the husband and explain the facts to him. In doing this, I think that the doctor can help a great deal, and I personally should have no hesitation, in certain circumstances, in stressing the possibility of congenital or even accidental infection as the origin of the woman's infection. It may be objected that my attitude towards the male and the female patient is inconsistent. I make no apology for it, and I feel fairly confident that those of you who have to do with the treatment of both sexes will understand. How often have we heard the pathetic excuse, "I can't come for treatment, my husband would get to know".

Continued observation

In the interests of the patient and of the extension of our knowledge of the subject, the observation period of late or latent syphilis should be a "life sentence". Provided, however, that the "vital systems" are apparently unaffected in the sixth decade of life, the necessary amount of this surveillance, in most cases, is minimal, and an annual interview is all that is necessary. With patients under 50 years of age, everything possible should be done to ensure that contact is maintained, particularly when the patient is a woman of childbearing age. Ritual (intermittent) courses of tablets of green mercurous iodide or of Hutchinson's pill (*Pilulae Hydrargyri cum Creta et Opii*), will often keep a patient attending who would otherwise default; if only for this reason, their use in some cases is justifiable. By this means I have kept many a patient under observation whom otherwise I assuredly should have lost.

The likelihood of default in all stages of syphilis depends upon the awareness of the patient of his condition. This awareness can be instilled only by the doctor, and that should be done as early as possible.

Signs of relapse

With regard to the primary—and later the periodical—examination of the latent syphilitic, although, in possibly early cases, signs of muco-cutaneous relapse will be sought for, what will concern us chiefly will be the condition of the two "vital systems". Here I should like to emphasize the importance of searching

for signs of leukoplakia on the tongue or the buccal mucous membrane. As well as being the occasional precursor of epithelioma, I consider this condition to be a fairly strong indication that infection is still active, and I have been struck by the frequency with which it is associated with symptoms or signs (clinical or radiographic) of cardiovascular disease.

It has been computed that subclinical aortic disease is probably present in 25 per cent of all so-called latent syphilitics, but that in most of these cases cure is attained by minimal treatment. The diagnosis of early cardiovascular syphilis is one of the physician's hardest tasks, and the patient and the radiologist (particularly the patient) will give him more help than will his stethoscope or sphygmomanometer. Too often all investigations yield negative results and the radiologist reports the heart and great vessels to be "within normal limits", although he cannot compare his picture with one taken 5-10 years previously.

Nevertheless, on cross-examination the patient may tell us of a slight substernal ache or pain, the onset of which was gradual and which may be becoming somewhat more insistent or frequent, although not necessarily more severe. The importance and significance of such a pain cannot be dismissed just because x-ray results and electrocardiographic readings are normal. I am assured by experts that, in the absence of coronary stenosis, electrocardiographic findings are most usually normal, although these normal findings will not exclude a patch of aortitis, perhaps quite adjacent to the coronary orifice.

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Cardiovascular syphilis

In no other condition is the maxim, *primum non nocere* more apposite, and not a few of us can recall instances in which treatment may have shortened rather than prolonged the life of our patients. Even in cases of apparently latent infection, the possibility of osteal involvement is incalculable. The rule always to commence the treatment of late or latent syphilis with bismuth and possibly iodides is a golden one. The danger of Herxheimer reactions after too strenuous initial treatment is well known, but that of therapeutic shock is perhaps not so well recognized, although careful cross-examination of patients will often elicit particulars of what were probably minor degrees of this complication. During the past 20 years I have not, to my knowledge, observed a fatal cardiac Herxheimer reaction, but I have seen 2 sudden deaths occurring within half an hour of an arsenical injection. The first was in a man aged 40 years, suffering from primary syphilis; he died after the seventh injection in ventricular fibrillation, the post-mortem findings being normal. The second occurred in a woman in the mid-forties; she was a latent syphilitic and died in an anginal attack 20 minutes after the third injection of neoarsphenamine; post-mortem findings were normal and multiple section of the coronary blood vessels and of the aorta did not show any pathological changes.

I can remember—and possibly some others can, too—a few cases of aortic incompetence in which the condition rapidly grew worse within a few weeks of the beginning of treatment. I cannot connect my cases with anything but gentle treatment, but I should consider that in certain circumstances therapeutic paradox occurs, as, for instance, when, as a result of treatment, chronically inflamed aortic valves "cicatrizate up" and, because of this shrinkage, become far more incompetent than ever. I see no reason why this should not take place as a result of any effective treatment, but fortunately it seems to be a fairly uncommon happening.

Once the condition is diagnosable the expectation of life in cardiovascular syphilis is poor; but so comparatively frequent are post-mortem signs of cardiovascular disease in elderly subjects in whom it was in no sense a cause of death, that it would seem that the over-all prognosis of syphilitic aortitis, even without treatment, is good. Moore considers that 70-90 per cent of all late syphilitics (in which category he includes latent cases) have unrecognized degrees of aortitis,

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and that in the great majority of these the process can be staved permanently by minimal treatment. In diagnosed aortitis without aneurysm or regurgitation, an expectation of 5-10 years can be doubled with treatment; in aortic regurgitation one of 2-3 years can be extended by 2, 3, or even more years; it is claimed that, even with moderate aneurysmal dilatation, the prognosis can be improved considerably by treatment.

General treatment.—The object of treatment, indeed, cannot be to eradicate infection, any more than it can be to restore already damaged structures. The comfort of the patient and the prolongation of life are paramount objectives. In view of this, general medical care is as important and more so than anti-syphilitic treatment. The nature of this medical care will depend upon the degree of cardiac involvement, and a careful assessment of this must be made as early as possible. When that has been done, the patient is told what he can and cannot do. Here again I would emphasize that syphilis must not be allowed to spoil lives, and that a moderate optimism, so long as orders are carried out, should colour what the patient is told. The truth, however, must be told to the relatives (without of course mentioning the specific cause), and for this reason the patient's private or panel doctor should be fully acquainted with the findings as soon as possible. Cases of early aortitis, uncomplicated by regurgitation or aneurysm, will need little regulation, provided that the cardiac reserve is adequate; moderate non-violent exercise usually can be allowed in the absence of praecordial or substernal pain or distress. When either of these is a constant symptom, the patient's activity must be restricted and, if the pain is in any way severe, nitrites, in the form of Tabella Glycerylis Trinitratis, should be administered freely. I have found that a couple of weeks' rest in bed every two or three months works wonders with these patients, and that the pain will often disappear for many weeks at a time.

Specific treatment.—I consider that all cases of cardiovascular syphilis should have some antisyphilitic treatment and that, generally speaking, unless there is evidence of renal disease, bismuth is the ideal drug for the purpose. Treatment should be prolonged and continuous, but, when insoluble suspensions of the metal or its salts are used, it can be given in courses of 10 injections, each course being followed by a month's rest. In advanced cases, or when the patient is over 60 years of age, I have found quinine iodobismuthate to be particularly well tolerated. The arsenicals, if used at all, should be reserved, I consider, for very early cases and not given when the patient is over 50 years of age. Their use is probably justified for patients in early middle age, with minimal radiological or clinical signs, whose condition has been diagnosed on the evidence of occasional attacks of pain and dyspnoea in the presence of positive serum reactions. It is essential, however, that at least two months' preparatory treatment with bismuth should first be given, that the initial dose of the arsenical should not exceed 0.15 gramme, that it should not rise above 0.45 gramme, and that administration should be stopped at once if pain or dyspnoea occur after treatment or are thought to be made worse by it.

In the present state of our knowledge (or shall I say ignorance?) of the action and effects of penicillin in late syphilis, it would be foolhardy to recommend this very powerful anti-spirochaetal substance, the rate of absorption of which cannot yet be properly controlled, for the treatment of cardiovascular syphilis. I note that so far the only published reports on its use in this condition have drawn attention to subsequent severe Herxheimer effects. I believe, nevertheless, that oral administration may prove eventually to be an efficient method of ensuring slow release of penicillin into the blood stream; if this comes about, its value may prove to be considerable. It is as well to remember that all antisyphilitic treatment is contra-indicated during threatening or actual heart failure and must be suspended until rest and digitalis have restored the *status quo*.

One is asked occasionally whether or not it is safe to give bismuth to hypertensive patients with albuminuria. My own experience has been that, provided that the albuminuria is not gross (a slight haze as distinct from a cloud), the drug

is not absolutely contra-indicated; I have seen cases in which the albuminuria cleared and the systolic blood pressure fell slightly after 6 months' treatment. It is impossible, however, to say whether this apparent improvement was *post hoc* or *propter hoc*. Here again, if its absorption could be carefully controlled, penicillin in gradually increasing doses might be the ideal treatment for such cases, but its day is not yet, if ever.

The advanced case.—Some of us, more especially those who work in hospitals in large cities, have numbers of well advanced cardiovascular syphilitic patients attending our clinics. Many of these unfortunates are alone in the world, some of them through their own fault, being unwilling to disclose their condition to relatives or even to a general practitioner. Although they are truly walking "in the valley of the shadow of death", the lives of many of them can be prolonged by careful management and treatment, and the necessity for periodical examination and assessment should be stressed. The provision of facilities for rest in bed, help at home, and temporary or permanent admission to suitable institutions can be facilitated by the social worker of the clinic in consultation with the medical officer. I know of a case at present of an elderly woman with a large aneurysm, living alone in a fifth-floor room, whose life would be completely changed were she brought to ground level. All this takes time and is difficult to accomplish in a busy overcrowded clinic, especially in one where the medical staff is working on a sessional basis, but it is well worth doing, whoever does it.

Neurosyphilis

It has been calculated that in about 25 per cent of all cases of untreated syphilis clinical neurosyphilis eventually develops, 5 per cent becoming parietic, 5 per cent tabetic, and 15 per cent exhibiting signs of meningo-vascular disease. Adequate treatment in the early stages will probably reduce this total figure to one of less than 5 per cent, but, according to Moore, the figures of the Cooperative Clinical Group indicate that the cerebrospinal fluid in about 15 per cent of otherwise latent cases shows pathological changes. These findings underline the importance of routine cerebrospinal fluid examinations in all late or latent cases, because, if these are postponed until treatment is "under way", the fluid may have become temporarily normal; treatment therefore may be stopped prematurely.

Asymptomatic neurosyphilis

How should cases of asymptomatic neurosyphilis be treated and what results can be expected? Much will depend upon the initial cerebrospinal fluid findings. The American classification of fluids into three types will be a rough guide to the amount of treatment probably necessary for the case in question and, indeed, to the ultimate prognosis. It has been my experience that the majority of Type I fluids, showing minimal abnormalities (cell count and globulin slightly increased, with all other findings, including Wassermann reaction normal) quickly revert to normal on routine treatment with trivalent arsenicals and bismuth, and that they remain normal for as long as the patient consents to stay under observation. Cases with Type III fluids (maximal changes with parietic Lange colloidal gold test curves) (in the complete absence of any psychological or neurological changes), in my experience, nearly always become normal in cell count and chemical tests, although the Wassermann reaction may remain positive for some years. The Cooperative Clinical Group (Stokes and his collaborators) estimates that only 40 per cent of these Type III fluids will become negative after 10 years.

Most cases of asymptomatic neurosyphilis show cerebrospinal fluid changes which are intermediate between these two extremes (Type II), and it has, I think, been the practice of most of us to treat them strenuously with arsenicals and bismuth for a minimum of 2 years and to be guided thereafter by the cerebrospinal fluid findings. In my opinion, a month's preliminary bismuth treatment should always be given to minimize the danger of a Herxheimer reaction. Provided that the cerebrospinal fluid is improving after 20 arsenical injections, I have been content to continue treatment with neoarsphenamine and bismuth. If, however,

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the improvement is inconsiderable or non-existent, a change to pentavalent arsenic is made. The cerebrospinal fluid is examined at three-monthly intervals and, if improvement does not then occur, malarial therapy is advised. Before the recent war I always advised all asymptomatic patients with parietic Lange formulae to submit to malarial therapy as soon as was possible. Now, however, having seen the good results of routine treatment in so many in the armed Forces, I am inclined to try trivalent arsenicals and bismuth in all of these cases and only then to advise malaria if no improvement is noted in the cerebrospinal fluid after 4-6 months. All of these patients, as also all those suffering from symptomatic neurosyphilis, should receive, after a short preparatory course of bismuth, a minimum of 4,000,000 units of penicillin in about a week. It may be that this dose is inadequate or that it is more than enough—some reports indeed suggest that the latter is the case—but, with a completely non-toxic drug, it is surely unwise, at this stage, to economize. Arsenical treatment is commenced at the same time, so as to give the patient the benefit of whatever synergistic action may exist between the two medicaments, and routine arsenical and bismuth treatment is continued for a minimum of one year after the cerebrospinal fluid reverts to normal. Here I am relying on impressions and a rather sketchy literature more than on personal experience; although speculation is interesting, it can also be deceptive.

Symptomatic neurosyphilis

Early meningo-vascular syphilis.—This condition is not very common but is sometimes encountered in patients who have defaulted after subminimal treatment. I well remember a young costermonger, who had defaulted after his second injection for primary syphilis, and who staggered into my clinic 18 months later with severe spastic paraplegia. These early cases of less than 5 years' duration may be treated strenuously from the outset; there is little danger of Herxheimer reactions and the results of treatment are usually, although not invariably, excellent. I should not now hesitate to give such patients penicillin, arsenicals and bismuth simultaneously, and, guided by the cerebrospinal fluid findings, should continue treatment for a minimum of 2 years.

Late meningo-vascular disease.—Preparatory bismuth treatment for 4-6 weeks is advisable, but the condition of the heart and great vessel cannot then be guaranteed; there is also a possibility of a local neurological "flare up" as the result of too strenuous initial treatment. I have heard already of a complete transverse myelitis closely following penicillin therapy.

The response of these patients to treatment is usually good but, as so many of them recover clinically without any treatment at all, it is difficult to be certain of its immediate value. It has been my experience that it is the exception for clinical recovery not to have taken place after a month's treatment with bismuth alone. Strenuous and prolonged treatment with arsenicals, bismuth and, perhaps, penicillin is necessary, and periodic examinations of the cerebrospinal fluid must be carried out. In the absence of (and sometimes in spite of) treatment, in appreciable numbers of patients of this type a parietic formula in the cerebrospinal fluid develops and a few ultimately become insane. If a parietic formula does develop in spite of arsenical and bismuth treatment, malaria therapy, penicillin or both is indicated; however, as is mentioned above, the time has now come when penicillin should be given to all patients as soon as it is considered to be safe to do so.

Parenchymatous neurosyphilis.—Although great hopes are now rightly entertained for penicillin as a therapeutic agent in parenchymatous neurosyphilis, particularly in early general paralysis, I should be inclined at this stage to use it in addition to orthodox treatment. All of us will agree that treatment must be as strenuous as is consistent with safety, and that its effects must be assessed constantly by means of periodical examinations of the cerebrospinal fluid. For many years now I have treated tabes with alternating courses of bismuth and

tryparsanide, and, on the whole, I have noted good results in the cerebrospinal fluid of such patients as have persevered with this treatment for 2 years or more. I have always felt uncomfortable about giving arsenicals in any form in cases of optic atrophy and hope that penicillin may prove to be a safe and efficient substitute for the arsenicals in this condition. It is especially encouraging to learn that the cerebrospinal fluid will often continue to improve for as long as 4 months after a standard course of from 2-4 mega units; sometimes, before improvement begins, there is an increase in the cell count and total protein with a temporary exacerbation of symptoms, such as lightning pains. Such reactions, in a condition so superlatively chronic as tabes, would seem to underline the exceptional potency of penicillin. Occasionally one is confronted with a patient with signs and symptoms of established tabes, but in whom the cerebrospinal fluid proves to be completely normal. The question then arises, "Should such a patient be treated and, if so, how?" In making a decision much will depend upon the age and sex of the patient and on the presence or absence of signs of syphilis elsewhere, especially in the cardiovascular system. Assuming, however, that, as is usually the case, the patient is in late middle age and presents no signs of cardiac involvement, generally speaking I should be against giving arsenicals or penicillin and should limit his treatment to bismuth alone, not so much in an attempt to influence the neurosyphilis, which, in such a case, is usually "burnt out", as to insure against the progression of any non-apparent co-existing aortitis.

General paralysis

I am refraining deliberately from dealing with the treatment of general paralysis. The recent papers by Drs. Nicol and Whelen in the *Journal* deal with this in a masterly fashion. Nicol has shown what can be achieved by systematic treatment with malaria and pentavalent arsenicals combined with energetic social work, and his evaluation of yet newer methods of treatment will be awaited eagerly by us all.

Late syphilis of the non-vital systems

With regard to late syphilis of the non-vital systems, although, as is well known, most lesions react rapidly to treatment, it seems to be held fairly universally that these patients need more strenuous and (up to the present) more prolonged treatment than do the simple latent cases. Nevertheless, I believe that this treatment should still be on an "insurance" basis and should not be carried on for an indefinite period. In view, however, of the presence of an actual lesion, which may be regarded as the "outward sign of inward disgrace", the policy must be loaded, and it has been my practice to give these patients twice the amount of treatment in double the period of time as is given to a patient with late latent syphilis. Thus, whereas between 20 and 30 injections of arsenicals and bismuth in 10-12 months should suffice for the latent case, the patient with certain forms of skin, bone or visceral syphilis is given twice that amount over twice the period. If the cerebrospinal fluid is normal before treatment, it is unnecessary to examine it again, but clinical observation, especially of the heart and great vessels, should be life-long. This used to amount only to a careful medical overhaul once a year for 5 years and thereafter every 2 years. Except in the rare event of relapse or the appearance of other evidence of clinical progression, further treatment will be needed only by women during their subsequent pregnancies, and, if this course is agreed to, marriage and childbearing may be allowed.

Marriage and childbearing.—With regard to marriage, we have to consider the likelihood or otherwise of the wage-earner's becoming a chronic invalid 10-15 years later. There is also the question, whether or not an insurance company will be willing to accept the life as an insurable one. All these points may be discussed with the patient and, if he is reasonably intelligent, the decision left to him. I am glad to notice that there is now an increasing reluctance on the part of insurance companies to refuse insurance to or to overload the policy of the well-treated

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syphilitic with apparently intact vital systems, even though the blood tests remain positive. This enlightened view is gaining ground in the United States of America, and though some British offices still maintain a very cautious attitude, the question is being studied afresh in the light of the efficiency of modern treatment and of the increased awareness by the public of the true facts about venereal diseases.

The unintelligent patient is hard to influence one way or another, and only too often the first that we hear of matrimonial aspirations is that pregnancy has occurred. It is as well to ask leading questions at an early stage. I remember, at the end of a long discussion on the pros and cons of marriage, a medical officer being more or less delated by a "bright young thing" who put the following question: "Why can't we get married now, as we have been living together for two years?" In dealing with these "types", my maxim, that "syphilis must not be allowed to spoil lives", is difficult to uphold, but liaison with the family doctor will often ensure that the offspring is adequately investigated and, in the rare cases in which it is necessary, that treatment is provided.

Therapeutic paradox.—In "non-vital" syphilis this is an occasional hazard. The manner and speed with which visible tertiary lesions respond to various types of treatment provides an excellent object lesson as to what will be the probable response of invisible ones. I can recollect a case of syphilitic cirrhosis of the liver, in which what I considered to be careful enough preparation with bismuth and iodides was followed by a severe ascites necessitating weekly paracentesis. An eventual Talma-Morison operation was not particularly successful. I have not met with syphilis of the stomach with hour-glass contraction after treatment, but I have seen the end-result of treatment of a possible gummatosis of the posterior mediastinum. The patient had grossly dilated superficial veins of the trunk and lower limbs, and I was assured by my teacher that this, with the radiographic opacity in the posterior mediastinum, indicated that the inferior vena cava had been strangled by the too rapid cicatrization of a healing gummatosis.

Herxheimer effects, except in the cardiovascular and occasionally the central nervous systems, rarely give any trouble. Obstruction of the air passage is said sometimes to follow too strenuous initial treatment in gumma of the larynx.

Penicillin in late syphilis

So rapid and favourable has been the response to penicillin of the late cutaneous manifestations of syphilis, that, although a decade must pass before its ultimate effect can be rightly evaluated, it seems to be fairly certain that all patients with late syphilis, with the exception of those with gross cardiovascular disease, should have the benefit of penicillin in addition to other forms of treatment. It is still impossible to say to what extent the traditional remedies can be replaced by penicillin; but if one may draw comparisons between it and the arsenicals and bismuth from their respective results in early syphilis, it seems that a dosage of about 3 mega units, given over a period of about a week, is therapeutically equal, if not superior, to about 20 injections each of standard amounts of arsenical and bismuth compounds. It is obvious that much work spread over a long time must be done before the place of penicillin in the treatment of late (and indeed early) syphilis can be designated accurately. Prolonged massive dosage, multiple courses and possibly combined treatment with aqueous solutions and slow-release preparations have yet to be tried and found wanting, before it can be said with certainty that penicillin alone cannot be relied upon. Up to the present it has been necessary to economize supplies, and present-day opinion as to the drug's worth in syphilis is based largely, if not entirely, upon the results obtained by treating many thousands of cases in the armed Forces in the field with dosages of 2,400,000 units.

In early syphilis, whether congenital or acquired, moderate doses of penicillin, with or even without a short course of an arsenical drug and bismuth, would seem to give results equal if not superior to those attained by time-honoured methods, with the added advantages that the treatment is considerably shortened and that the risk of toxic effects is greatly reduced.

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In late syphilis the position is more obscure and, until the equivalent therapeutic values of penicillin, the arsenicals and bismuth have been determined more accurately, it will not be possible to utilize to the full the accumulated experience of the past 25 years. Meanwhile, as new preparations and dosage schemes are tried, it is to be hoped that the necessity for long and careful follow-up will be impressed upon both doctors and patients, and that propaganda will bring this to the notice of the public. As it has been rightly said (Moore): "We are still in the process of learning how to use this drug. We do not know yet and it is going to be some time before we are sure."

Conclusions

My own feelings on the subject can be summarized as follows.

(1) The management and treatment of late syphilis can never be a matter of routine. Ready-made schemes will not do; they must always be "made to measure".

(2) Syphilis, if possible, must not be allowed to spoil lives. Although inadequate treatment can do this, unnecessarily prolonged treatment can have the same result.

(3) The objects of treatment should be as follows.

(a) The healing of lesions, the relief of symptoms and the prevention of the transmission of infection.

(b) The maintenance of good health and the prevention of progression or relapse.

(c) Least important of all, serological reversal. If a patient can be maintained in or restored to health, sero-resistance can be regarded as something analogous to a positive Mantoux or Widal test in a patient recovering from tuberculosis or typhoid fever.

Although acknowledgments are not customary in an address such as this, it would be churlish not to acknowledge my indebtedness to my teachers, especially to my first teacher, Colonel Harrison who, many years ago, initiated me into the "art and mystery" of venereology; to the authors of the standard British and American text-books; to numerous writers of papers; and finally to my colleagues, both in the armed Forces and in civil life, who have helped me to make up my mind, at all events, on some aspects of this far from facile subject.

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